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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)



Applicant's or agent's file reference PV/326/PCT	FOR FURTHER ACT	1 Tollinary Distriction
International application No.	International filing date (da	ay/month/year) Priority date (day/month/year)
PCT/CZ 03/00058	21.10.2003 ⁻	24.10.2002
	PC) or both national classification and	nd IPC
Applicant ZENTIVA, A.S. et al.		
This international prelimir Authority and is transmitted	nary examination report has been ed to the applicant according to A	n prepared by this International Preliminary Examining Article 36.
1	f a total of 4. sheets, including this	
	accompanied by ANNEXES, i.e. s I are the basis for this report and d Section 607 of the Administration	sheets of the description, claims and/or drawings which have for sheets containing rectifications made before this Authority ive Instructions under the PCT).
These annexes consist of	of a total of 5 sheets.	· · · · · · · · · · · · · · · · · · ·
1.00		
3. This report contains indi	cations relating to the following ite	ems:
🛛 Basis of the	opinion	
II Priority		, , , , ,
III Non-establis	hment of opinion with regard to no	novelty, inventive step and industrial applicability
IV D Lack of unity	of invention	•
V M Decembed st	tatement under Rule 66.2(a)(ii) wi I explanations supporting such sta	oith regard to novelty, inventive step or industrial applicability; catement
VI 🔲 Certain docu		•
. VII Certain defe	cts in the international application	n
VIII Certain obse	ervations on the international appl	blication
Date of submission of the demar	id	Date of completion of this report
09.04.2004		05.11.2004
Name and mailing address of the preliminary examining authority:		Authorized Officer
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/CZ 03/00058

1	. в	Basis	of	the	re	por	t
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 With regard to the elements of the international application (Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)):

	Desci	ription, Pages					
	1, 2, 6	6-14	as originally filed				
	3-5		received on 17.04.2004 with letter of 09.04.2004				
	Clain	ns, Numbers					
	1-6		received on 17.04.2004 with letter of 09.04.2004				
2.	With langu	With regard to the language , all the elements marked above were available or furnished to this Authority language in which the international application was filed, unless otherwise indicated under this item.					
	Thes	e elements were ava	ilable or furnished to this Authority in the following language: , which is:				
		the language of a trai	nslation furnished for the purposes of the international search (under Rule 23.1(b)).				
	п.	the language of publication of the international application (under Rule 48.3(b)).					
,,		the language of a tra Rule 55.2 and/or 55.3	nslation furnished for the purposes of international preliminary examination (under 8).				
3.	. With inter	regard to any nucle national preliminary e	otide and/or amino acid sequence disclosed in the international application, the examination was carried out on the basis of the sequence listing:				
	Π.	contained in the inter	mational application in written form:				
		filed together with the	e international application in computer readable form.				
			ntly to this Authority in written form.				
	П	furnished subsequer	otly to this Authority in computer readable form.				
		The statement that t	he subsequently furnished written sequence listing does not go beyond the disclosure polication as filed has been furnished.				
		The statement that the listing has been furn	he information recorded in computer readable form is identical to the written sequence				
4	. The		resulted in the cancellation of:				
		the description,	pages:				
		the claims,	Nos.:				
		the drawings,	sheets:				
ţ	5. 🗆	been considered to	n established as if (some of) the amendments had not been made, since they have go beyond the disclosure as filed (Rule 70.2(c)).				
		(Any replacement s report.)	heet containing such amendments must be referred to under item 1 and annexed to this				
	6. Ad	ditional observations	, if necessary:				

INTERNATIONAL PRELIMINARY **EXAMINATION REPORT**

International application No.

PCT/CZ 03/00058

- V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- 1. Statement

Novelty (N)

Yes: Claims

1-6

Inventive step (IS)

Yes: Claims

No:

No:

1-6

Claims Claims Yes:

Claims

1-6

Claims No:

2. Citations and explanations

Industrial applicability (IA)

see separate sheet

The amendments filed with letter dated 9-04-04 are in conformity with the requirements of Article 34 PCT. New claim 1 is supported by a combination of original claims 1 and 3 with a passage of page 5, lines 4-8.

The application now concerns a process in 4 steps for making an optically active rivastigmine of formula II.

- D1: CHEN CHUNG-PIN: TETRAHEDRON LETTERS, vol. 32, no. 49, 1991, pages 7175-7178, XP009025296
- D2: US-A-5 602 176 (ENZ ALBERT) 11 February 1997 (1997-02-11)
- D3: CISZEWSKA GRAZYNA: J.LABELLED COMPD.RADIOPHARM., vol. 39, no. 8, 1997, pages 651-668, XP002269029
- D4: EP-A-0 193 926 (YISSUM RES DEV CO) 10 September 1986 (1986-09-10)

D1 discloses the optically active the S-m-hydroxyphenylethyldimethylamine (key intermediate in the present process).

D2 discloses the resolution of racemic rivastigmine with a tartrate salt.

D3 discloses a process for making optically active rivastigmine by asymmetric reduction. to obtain the methoxy intermediate.

D4 discloses the formation of rivastigmine by reaction of carbamoyl chloride with the hydroxy intermediate (last step in present process).

D3 which is the closest prior art differs from the presently claimed process by the fact that the asymmetric carbon is introduced though an asymmetric reduction to get the Sm-methoxyphenylethyldimethylamine, which is demetylated to obtain the S-mhydroxyphenylethyldimethylamine (see p.655, reaction scheme cpd15 -->cpd 19), while the presently claimed process makes a resolution of the racemic mhydroxyphenylethyldimethylamine intermediate.

No other document discloses nor suggest the resolution of this intermediate to get the optically active rivastigmine.

The skilled person would have no indication in the prior art to use such a solution in order to develop an alternative process for the preparation of optically active rivastigmine.

CLAIMS

1. A method of production of (-)-(S)-3-[1-(dimethylamino)ethyl]phenyl-N-ethyl-N-methylcarbamate, i.e. rivastigmine of formula Π

or of its hydrogentartrate of formula I

characterized in that the compound of formula Π

optionally its alkali salt, is reacted with a compound of formula VII

wherein X is a leaving group resulting in the compound of formula II, which is then optionally converted, by reacting with tartaric acid, into the compound of formula I.

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ART 34 AMOT

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- 2. The method according to claim 1 characterized in that the compound of formula III is converted, by reacting with a strong base, into an alkaline salt, which is subsequently reacted with the compound of formula VII.
- 3. The method according to claim 1 or 2 characterized in that the compound of formula III is obtained by transforming methoxyacetophenone of formula VI

into racemic amine of formula IV

which is further resolved by reacting with an optically active acid, whereafter the desired respective diastereoisomer is crystallized and finally converted into the compound of formula III.

4. The optically active compound having absolute configuration (S) of formula III

by reacting with an optically active acid, crystallizing the respective diastereoisomer and subsequently isolating the optically active phenol III.

The racemic phenol of formula IV can be obtained by reductive amination of methoxyacetophenone of formula VI

and subsequent O-dealkylation of the compound of formula V

The reductive amination is carried out by means of dimethylamine or its hydrochloride and a reduction agent, usually a hydride such as sodium borohydride.

The O-dealkylation agents can be selected from among strong acids, such as for example hydrobromic acid, or from among boron halides, such as boron bromide.

As is demonstrated in the examples of especially preferred embodiments, the present method makes it possible for obtaining the product of formula I in an especially high optical purity. A reproduction of the method known so far, even with recrystallization, has not resulted in obtaining such high optical purity.

It further results from comparison that use of the optically active compound of formula III results in lowering of the consumption of the expensive and carcinogenic N-ethyl-N-methylcarbamoylchloride (corresponding to general formula VII for X = Cl) by 2/3.

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which is, optionally in the form of its alkali salt, reacted with a carbamoylhalide of formula VII

wherein X is a leaving group.

The resulting compound of formula II

is converted, by reacting with tartaric acid, into the respective salt of formula I.

Advantageously, the phenol of formula III is converted with a strong base in an inert solvent into the phenolate and it is reacted with the carbamoylhalide of formula VII.

As the strong base, hydrides of alkali metals, such as sodium hydride, or alkyl lithium compounds such as butyl lithium, can be used. The inert solvent is preferably chosen from the group of dialkyl ethers such as tetrahydrofuran or 1,2-dimethoxyethan.

The respective optically active phenol of formula III has not been described yet and it can be obtained by resolving the racemic phenol of formula IV

REPLACED BY ART 34 AMDT formula VII (mostly specifically N-ethyl-N-methylcarbamoyl chloride) in an about 300% excess is another drawback

Resolution in an earlier stage of the synthesis appears, at first sight, as desirable, but far from being feasible. There remains the question whether it is possible to obtain enantiomerically pure intermediates and, especially, whether these products can be used for further synthesis without being subject to racemization. The necessity of recrystallization would cast doubts on advantageousness of such procedure.

It has now turned out that optically resolving the intermediate products (i.e. performing the operation in an earlier stage of production) and performing the final step with an optically active substance, permits to obtain a very good yield of (S)-rivastigmine with retaining high analytic purity.

Disclosure of Invention

The present invention consists in a method of production of (-)-(S)-3-[1-(dimethylamino)ethyl]phenyl-N-ethyl-N-methylcarbamate (rivastigmine) of formula II

or of its hydrogentartrate of formula I

starting from the optically active phenol of formula III

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